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| 10/009,579 | 03/22/2002 | Lou Franciscus M. H. De Leij | Rijk-15(P52075US00 | 1723 |

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| EXAMINER | |
|---|---|
| QIAN, CELINE X | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/009,579 | DE LEIJ ET AL. | |
| | Examiner | Art Unit | |
| | Celine X Qian Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *11-13 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-18 are pending in the specification.

### *Election/Restrictions*

Applicant's election with traverse of Group I in the reply filed on 11/5/04 is acknowledged. The traversal is on the ground(s) that the common technical concept is novel, thus link the invention of all groups as a whole. Applicants assert that the common technical feature is the novel non-aqueous epithelial specific promoter, which is a subgroup of the epithelial tumor or a subgroup of all tumors. Applicants argue that the carcinoma specific promoter taught by Chen et al. DF3/MUC1 cannot be considered as a non-squamous epithelial cell specific. Applicants further cited Cooper et al. and Abe et al. to support the notion that MUC1/DF3 does not meet the requirements for specificity. Applicants thus conclude that the lack of unity requirement is erroneous.

The above arguments have been fully considered but deemed unpersuasive. As discussed in the previous office action, the special technical feature of is a promoter or fragment thereof that is carcinoma selective. Although Applicants indicate that the promoter is non-squamous epithelial cell specific, the claims do not have the "non-squamous epithelial cell specific" limitation. As such, the DF3/MUC1 promoter disclosed by Chen et al. clearly anticipates this special technical feature of a carcinoma selective promoter. Therefore, the unity of the invention does not exist.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 11-13, 15-18 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-10 and 14 are currently under examination.

### *Sequence Compliance*

This Application is not in sequence compliance. The nucleic acid sequence in Figure 1 and on page 15 lack sequence identifier.

### *Claim Objections*

Claim 6 is objected to because of the following informalities: the word "inducable" appears to be a mis-spell of "inducible." Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 10 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 10 is directed to a host cell comprising an isolated nucleic acid, which is a product of nature that is not a statuary subject matter.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 14 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite an isolated nucleic acid comprising a tissue specific promoter or functional fragment thereof which directs selective gene expression in carcinoma cells. Such recitation potentially encompasses a large number of nucleic acid molecules of varying structure and sizes that have the function of direct carcinoma selective gene expression. However, the specification only teaches a 4.2 kb region at 5' of the GA733-2 gene and several fragments within this region that confers expression in SW948, an adenocarcinoma, and COS-7, but not in FLF (human fetal lung fibroblast) and HUVEC (human

umbilical veins). The specification fails to teach whether these fragments are lung carcinoma specific (as recited in claim 2). The specification also fails to teach regulatory regions of other genes of "functional equivalent" or "functional fragment" thereof that have claimed function of being carcinoma or lung carcinoma selective. The specification also fails to teach what structural elements the claimed genus of nucleic acids must share for them to possess the claimed function. As such, the structural and functional relationship of the claimed genus of nucleic acids is missing.

The claims further recite a functionally equivalent of a nucleic acid has sequence of –778 to –422 as shown in Figure 1 (claim 3), a functional fragment of an inducible or suppressible promoter (claim 6), and a functional fragment of a suicide gene (claim 7). Similarly, the specification fails to disclose any functional equivalent of a nucleic acid having the sequence from –778 to –422 as shown in Figure 1, a functional fragment of an inducible or suppressible promoter or a functional fragment of a suicide gene. As such, the structural relationship between the claimed nucleic acid and their function is missing. Therefore, the specification fails to disclose a representative number of species by their complete structure nor their identifying characteristics. Thus, the written description requirement is not met.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a medicament comprising an isolated or recombinant nucleic acid comprising a tissue specific promoter or functional fragment that directs gene expression in a carcinoma selective manner.

The breadth of the scope is broad. The claim encompasses a medicament of any kind that comprises a tissue specific promoter that directs expression in carcinoma cells.

The teaching of the specification is limited. The specification fails to teach what disease(s) the claimed medicament can treat. The disclosure of the instant specification only prophetically teaches that the claimed promoter can be used in gene therapy to treat cancer, but does not teach specific steps for this claimed embodiment. As such, one skilled in the art would have to rely on the teaching of the prior art to use the claimed invention.

The state of art at the time of filing considers the success of gene therapy as unpredictable. Verma et al. (1997, Nature, Vol. 389, pages 239-242), Anderson et al.(1998, Nature, Vol. 392, pages 25-30), and Palu et al.(1999, Journal of Biotechnology, Vol. 68, pages 1-13) discuss the inherent difficulties in gene therapy. The major difficulties include poor delivery systems and poor gene expression after delivery (see Anderson, page 30, 1st col., 5th paragraph). In *ex vivo* gene therapy, transcriptional silencing is an obstacle that prevents sufficient gene expression to achieve therapeutic level. In addition, efficient transplantation is another challenge to *ex vivo* gene therapy. As Verma et al. indicate that attempts to repeat long-term myoblast transplantation in hemophiliac dogs led to only short-term expression because the infected dog myoblasts could not fuse with the muscle fibers (see page 240, 3rd col., 1st paragraph). Although hematopoietic system may offer an advantage for *ex vivo* gene therapy because resting stem cells can be stimulated to divide *in vitro* using growth factor and the transplantation technology is well

established, there is still a lack of good enhancer-promoter combination that allow sustained production of high levels of protein in these cells (see Verma, page 240, 3rd col., 1st paragraph). Another factor that affects the efficacy of gene therapy methods is the immune system of the host organism (see Palu, page 9, 1st col., 2nd paragraph, lines 1-5). The host immune system rejects the foreign cell that is introduced to said host thus prevents the expression of the gene within the cell. Therefore, in view of the above technical difficulties, one of skilled in the art would have to rely on the teaching of the specification to use the medicament to treat cancer.

However, the specification does not provide teachings that would overcome the problems discussed above. Without teaching from the specification and lack of guidance from the prior art, one skilled in the art would have to engage in undue experimentation to make and use the claimed invention as claimed. Therefore, the claim is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-10 and 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-10 and 14, the recitation of "essentially carcinoma selective" renders the claims indefinite because it is unclear what degree of selectiveness constitutes "essentially carcinoma selective." As such, the metes and bounds of the claim cannot be established.

Regarding claim 4, the word "derived" renders the claim indefinite because the nature and number of derivative process is unknown. As such, the metes and bounds of the claim cannot be established.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (J.Clinl. Invest., 1996).

The claims are drawn to a nucleic acid comprising a tissues specific promoter that directs carcinoma selective expression, a nucleic acid comprising said promoter and a nucleic acid of interest, a nucleic acid comprising said promoter and a suicide gene, a vector comprising said nucleic acid, a gene delivery vehicle comprising said nucleic acid and a host cell comprising said nucleic acid.

Chen et al. disclose a DF3/MUC1 promoter that is capable of direct tissue specific and carcinoma selective expression (see page 2539, 2nd col., 2nd paragraph, lines 15-20). Chen et al. disclose an adenoviral vector (a delivery vehicle) comprising said promoter and a HSV-tk gene (a nucleic acid of interest and a suicide gene). See page 2543, 2nd col., 3rd paragraph, and Table III. Chen et al. further teach said vector is transduced into CD 34+ progenitor cells (Table III). Therefore, Chen et al. disclose the instantly claimed inventions.

Claims 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Siemieniako et al (1992, BBRC, Vol.186, No.3).

The claims are drawn to a nucleic acid comprising a tissue specific promoter that is able to direct carcinoma selective gene expression and comprises a nucleic acid from –778 and –422 shown in Figure 1, wherein said nucleic acid is isolated from human.

Siemieniako et al. disclose a promoter of 17-1A antigen. The promoter comprises –1000 to transcription start site (see Figure 1A). The nucleic acid molecule shown in the Figure of the instant application is also 5' region of the gene encoding 17-1A antigen. Although the reference does not teach the sequence of the promoter, the disclosed sequence nevertheless comprises the –778 to –422 region, and inherently has the same function. Absent evidence from the contrary, Siemieniako et al. disclose the instantly claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER